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NTP Board of Scientific Counselors' Report on Carcinogens Subcommittee
c/o Dr. Larry G Hart, Executive Secretary
NIEHS
Research Triangle Park, NC

Re: RC Draft Background Document for TCDD

Dear Subcommittee Members:

As a cancer epidemiologist who has followed the literature on the carcinogenicity of dioxin with considerable interest, I have been asked by the American Forest and Paper Association to review the document referenced above, as well as the updated study of the Seveso cohort that was distributed with the document. My comments are attached. I hope you will find them helpful in your deliberations.

Yours sincerely,

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Seattle, WA

Comments on "RC Draft Background Document for TCDD"

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This document lays out the rationale for a proposed listing of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) as a known human carcinogen. It relies heavily on a recent International Agency for Cancer Research (IARC) monograph (Vol 69, 1997) that classified TCDD as a Group 1 carcinogen (i.e., TCDD is carcinogenic to humans). The IARC committee found the epidemiologic evidence to be limited, and in its conclusion, the committee relied heavily on the carcinogenicity of TCDD in experimental animals and on mechanistic considerations. Although I have a number of concerns about the interpretation of the epidemiologic data in the IARC monograph, I will restrict my comments here to the use of the monograph to support the conclusions in the RC draft document.

In my opinion the RC draft document overstates the epidemiologic conclusions of the IARC monograph. On pages RC-1 and 3-2 the draft document says that the IARC monograph noted a causal relationship between TCDD exposure and mortality from all cancers combined. In fact, the IARC monograph does not make the claim of a causal relationship in the epidemiologic data. The monograph concludes that the observed association between exposure to TCDD and all cancers combined is unlikely to be due to chance or confounding, although confounding by other occupational exposures cannot be ruled out. The evidence for a dose-response relationship is noted to be weak, however. Furthermore, the strength of association is noted to be low. Thus, two of the crucial criteria for inferring causality in epidemiology (dose-response and strength of association) are not currently met by epidemiologic studies of TCDD.

The RC draft document relies also on a recent paper by Bertazzi et al., which is currently in press, commenting that "these additional findings were not considered in the IAEC evaluation and further strengthen the association between dioxin exposure and human cancer." After careful reading of the paper I conclude, however, that the evidence is equivocal, at best. In fact, the Bertazzi paper does not support some of the key conclusions in the IARC monograph.

Bertazzi and colleagues describe a continuing follow-up of a cohort of individuals exposed to TCDD following an industrial accident in Seveso, Italy. The contaminated area was divided into three zones (A, B and R, in descending order of contamination), and mortality of the residents of these areas followed from 1976 to 1991. The population of a surrounding non-contaminated area was used as a reference group. The results are reported in a series of tables in the paper. The IARC monograph concluded that, in epidemiologic studies, TCDD was more strongly associated with total cancer than with cancer at any specific site. This conclusion is not supported by the Bertazzi paper which

finds absolutely no indication of an association of TCDD with total cancer in either males or females. Tables 3 and 4, which report the observed and expected number of cancers at specific sites show excesses at some sites and deficits at others, just the kind of random pattern that would be expected if TCDD exposure were not associated with cancer. Furthermore, for the cancers that are elevated, there is no consistency with regard to sex or level of exposure. For example, carcinoma of the rectum is elevated in males resident in zone B, but is not elevated among males in zones A and R or among females in any zone. Finally, the cancers that are elevated in the Seveso cohort are not elevated in the occupational cohorts reviewed in the IARC monograph. I believe that the Bertazzi study is consistent with the view that TCDD exposure is not associated with cancer in that cohort.